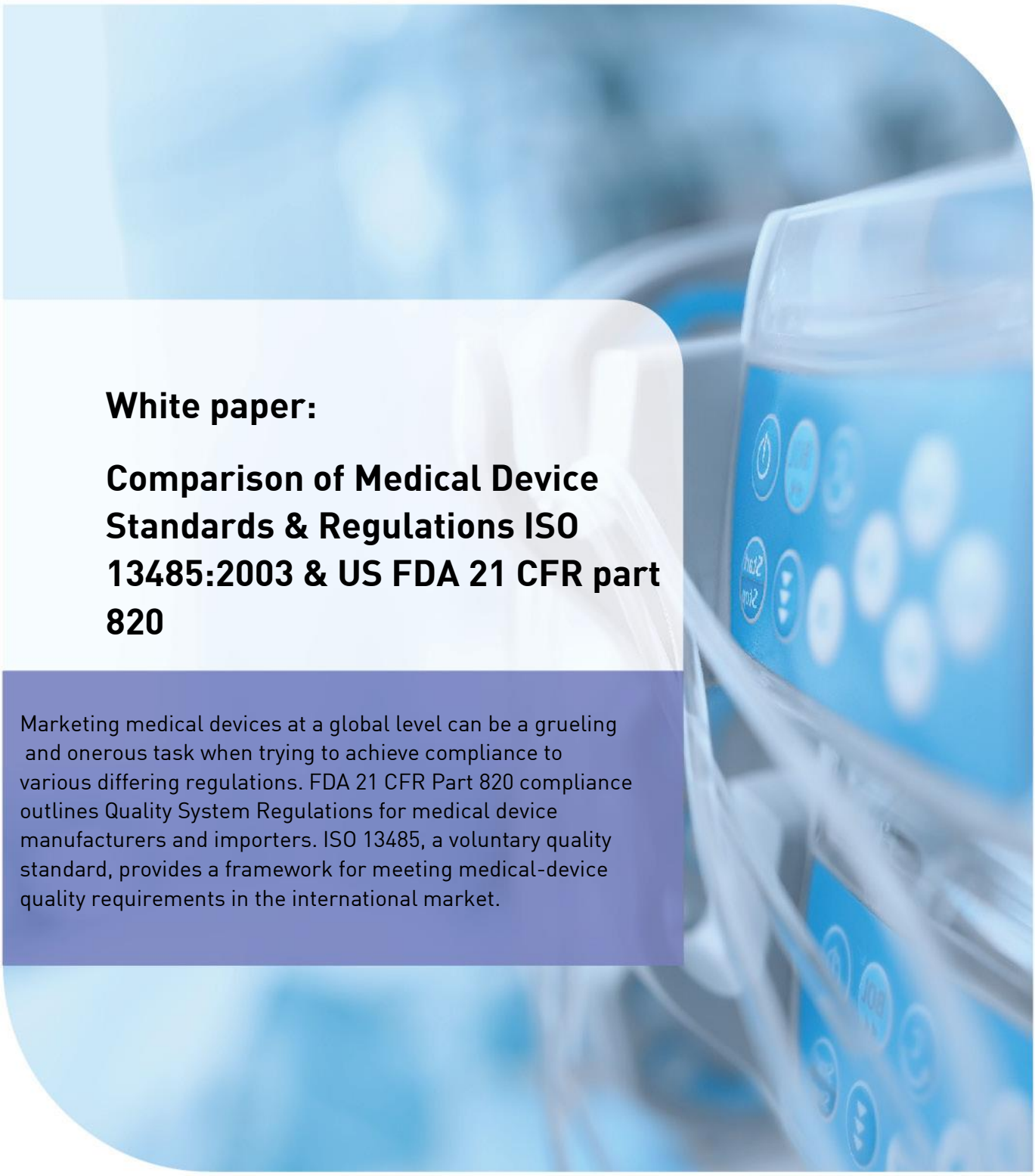

White paper:

Comparison of Medical Device Standards & Regulations ISO 13485:2003 & US FDA 21 CFR part 820

Marketing medical devices at a global level can be a grueling and onerous task when trying to achieve compliance to various differing regulations. FDA 21 CFR Part 820 compliance outlines Quality System Regulations for medical device manufacturers and importers. ISO 13485, a voluntary quality standard, provides a framework for meeting medical-device quality requirements in the international market.

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Introduction

Medical device manufacturers around the world are regulated to ensure that their product conformity is safeguarded. In order to do this, manufacturers need a well-structured quality management system. Manufacturers are required to not only establish specifications for their products and processes, but also to put quality systems in place to ensure those requirements are met. They are also responsible to ensure they have the objective evidence of meeting quality system (QS) requirements.

The FDA Regulation

During the 1990s, the FDA Regulation was the most sought-after document with regards to current Good Manufacturing Practice (cGMP) requirements for medical device organisations.

For FDA-regulated products, Part 820 of Title 21 of the Code of Federal Regulations (CFR) outlines quality system and cGMP regulations for medical device manufacturers to ensure that the devices are safe and effective.

The FDA stipulates QS requirements in their regulation, but has left it up to the manufacturers to determine which sections are relevant to their specific products and processes, and to determine the ways they intend to meet the QS requirements.

The FDA QS regulation is applicable to finished medical devices sold commercially in the USA, including devices that are imported. According to 21 CFR 820.3(l), a finished device is defined as "any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labelled, or sterilised". Even accessories to finished devices, such as blood tubing and diagnostic x-ray components, are subject to the QS regulation.

There are some types of medical devices that the FDA has considered to be exempt from certain GMP requirements, but exempt manufacturers are still expected to keep compliant files and design control records.

The ISO Standard

ISO 13485:2003 is currently the most comprehensive standard detailing management system requirements for medical device manufacturers, and has been gaining popularity since the late 2000s. It specifies requirements for organisations providing medical devices to meet customer requirements and relevant regulatory requirements.

The ISO standard is a global standard that aims to harmonize medical device regulatory requirements for quality management systems. While this standard is mandatory in countries selling products in markets in the European Union, it is not enforced by the US Food and Drug Administration (FDA).

Quality Management System (QMS)

The ISO standard derives its content from ISO 9001:2000, whereas the FDA regulation is based on the 1994 version of ISO 9001. While ISO 13485:2003 and FDA 21CFR Part 820 may appear similar in their QMS requirements, they are not completely harmonized.

> *"This international Standard is based on a process approach to quality management. Any activity that receives inputs and converts them to outputs can be considered as a process. For an organization to function effectively, it has to identify and manage numerous linked processes."* – ISO 13485
>
> *"This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance" – 21 CFR Part 820 Quality Systems Regulation*

An obvious difference between the ISO standard and the FDA regulation with respect to general QMS requirements is that the standard requires a more process-based approach, with specific emphasis on outsourced processes. On the other hand, the FDA regulation has more stringent reporting requirements.

A review of both documents has identified some major topics that are more explicitly detailed in the standard or the regulation respectively, as shown in the following table:

ISO 13485:2003	FDA 21 CFR Part 820
Quality Manual	DMR and DHR
Management review	Resources and Infrastructure
Customer focus	Production and process controls
Product realization, design and development	Monitoring and measurement of product
Monitoring and measurement of processes	Improvement
	Traceability

Quality Manual

The ISO standard has a specific requirement for manufacturers to have a Quality Manual, but the FDA regulation does not. This means that quality manuals are a common occurrence outside the US and with non-FDA regulated organisations.

Management Review

Both the ISO standard and the FDA regulation require regular management reviews to be conducted to ensure that the quality objectives are met. However, the ISO standard is more explicit regarding review inputs (e.g. audit results, CAPA status, customer feedback, new or revised regulatory requirements) and review outputs (e.g. improvements to QMS and its processes, improvements to product, resources). The FDA regulation considers review inputs and outputs to be logical and does not categorically list them out.

Device Master Record (DMR) and Device History Record (DHR)

The terms DMR and DHR are not found anywhere in the ISO standard. These terms, only used by the FDA, describe technical files expected to be kept by FDA-regulated medical device manufacturers. The ISO standard requires manufacturers to keep records of the contents that are typically found in a DMR and DHR - product and process specifications, procedures, packaging and labelling specifications, maintenance methods, manufacture records, etc. – but without the need for them to be located together in a specifically labelled file.

Customer Focus

ISO13485 tends to be more focussed on customer requirements than the regulation. The latter solely concentrates on meeting requirements related to the design, manufacture and distribution of the medical devices, whereas the standard has specific requirements to ensure customer satisfaction throughout the entire product lifecycle.

Resources and Infrastructure

The FDA regulation is more explicit about resources and infrastructure than the ISO standard. The regulation specifies that personnel should be trained on device defects potentially arising from improper job performance or during verification and validation activities. In addition, it contains specific requirements related to inspections, equipment adjustments, maintenance schedules and manufacturing materials.

Product Realization

Product realization is not explicitly recognized in the FDA regulation, unlike the ISO standard, which includes the requirement for risk management records to be maintained throughout the process of product realization planning. This can be identified as a significant strength in the ISO standard over the regulation, in efforts to minimise manufacturing and other process–related risks on the product. Further guidance on the application of risk management to medical devices can be obtained from ISO 14971:2007.

Product Design and Development

The ISO standard applies product design controls to all medical devices whereas the FDA regulation limits the control to more high risk devices including Class II, III and specific Class I devices.

Both documents have consistent objectives with regards to the design and development planning and outputs, review and verification. However, they contain slightly different requirements for design and development inputs. The FDA regulation specifies user and patient needs to be addressed as design and development inputs, while the ISO standard lists additional inputs such as statutory requirements, information from previous similar designs, and the output(s) of risk management. This further highlights the significance of risk management required by ISO 13485 during product realization planning.

The FDA regulation calls for risk analysis during the design and development validations stage. This is inconsistent with the ISO standard, which explicitly requires that risk management activities be performed during all stages. Furthermore, the expectation from the ISO standard is that the validation activities must be conducted before product delivery or implementation. For cases where validation can only be performed after the product is assembled and installed at the customer site, the standard also provides further consideration regarding the completion of product "delivery".

With respect to design changes, the ISO standard contains specific requirements for evaluation of change on products already delivered. This is not mentioned in the FDA regulation.

Production and Process Controls

The FDA regulation is more specific than the standard on controlling production and process changes, labelling activities, and preservation of product, including packaging, handling, storage and distribution. The former also requires review of validated processes when change or deviations occur during production.

On the other hand, the ISO standard includes some general traceability requirements that are not found in the FDA regulation. The standard also requires identification and traceability of product returned to the organization, and specifies requirements for control of customer property while it is in use or held by the organization.

Monitoring and Measurement of Processes

The ISO standard has a greater emphasis on monitoring and measurement of processes than the FDA regulation. The latter mainly focusses on product but briefly mentions process analysis among other requirements for establishing and implementing corrective and preventative actions. However, the ISO standard specifically requires that quality management system processes be monitored and measured to ensure expected results and product conformity are achieved.

Monitoring and Measurement of Product

With regard to product monitoring and measurement, the FDA regulation stipulates more detailed requirements regarding sampling plans and their validity. It emphasizes the need for basing sampling plans on statistical rationale, which means the manufacturer is expected to develop valid statistical techniques for controlling and verifying process capability and product characteristics.

Improvement

The ISO standard and the FDA regulation are consistent in the use of corrective and preventative actions (CAPAs) as a means of QMS improvement. However, the regulation has more specific requirement regarding complaints handling and documentation.

Traceability

Traceability requirements in the regulation are geared towards surgical implant devices, whereas the standard allows the manufacturer to determine the level of traceability for their devices.

Process Validation

"The organisation shall validate any processes for production and service provision where the resulting output cannot be verified."

"Validation shall demonstrate the ability of these processes to achieve planned results." – ISO 13485

"Each manufacturer shall establish and maintain procedures for changes to a specification, method, process or procedure. Such changes ***shall be verified or where appropriate, validated*** *before implementation and these activities shall be documented."*

"Where the results of the process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures." – 21 CFR Part 820

Much emphasis is put on the topic of Process Validation in both the standard and the regulation. regulation. The requirements are essentially similar.

The FDA Regulation includes additional emphasis on verification and/or validation of changes to production and process. The FDA uses a lifecycle approach when it comes to process validation. Their requirements involve a series of activities over the lifecycle of the process, starting with process design. Process design fuels the process qualification activities, and continued process verification feeds back into process design.

Summary

In summary, the FDA 21 CFR 820 regulation and the ISO 13485 standard are not fundamentally disparate. Generally, organisations that have experience complying with one will feel comfortable with the other.

Currently, it is primarily the US that relies on the FDA regulation for compliance and regulatory requirements, whereas the EU, Canada, Japan, Australia, and New Zealand follow the ISO standard closely. Medical device organisations in the remaining countries tend to either rely on just the standard or use both the standard and the regulation.

References

International Standard ISO 13485:2003, Medical Devices – Quality management systems – Requirements for regulatory purposes

Title 21, Food and Drugs Code of Federal Regulations, United States Department of Health and Human Services, Food and Drug Administration Part 820, Revised as of April 1, 2011

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net

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Our team includes international GMP experts who have previously held leadership roles within regulatory bodies.

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